PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant:	Nobuto YAMAMOTO		
Serial No:	09/826,463	Group Art Unit:	1647
Filed:	April 5, 2001	Examiner:	David S. Romeo
Att. Docket No.:	Y1004/20017	Confirmation No.:	2419

For: PREPARATION OF POTENT MACROPHAGE ACTIVATING FACTORS DERIVED FROM CLONED VITAMIN D BINDING PROTEIN AND ITS DOMAIN AND THEIR THERAPEUTIC USAGE FOR CANCER, HIV-INFECTION AND OSTEOPETROSIS

LETTER

Mail Stop Appeal-Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Attached is a Brief On Appeal, which replaces the Brief On Appeal that was filed in the United States Patent and Trademark Office on June 11, 2004, with regard to the above-captioned matter.

One typographical error was corrected as follows:

MAP to MAF, page 2, second paragraph, line 9.

Also we are attaching: In re Vaeck, U.S. Court of Appeals Federal Circuit, 20 USPQ2d 1438.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

June 28, 2004

By_____
Robert S. Silver
Registration No. 35,681
Customer No. 03000
(215) 567-2010
Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 165.00

Complete if Known	
Application Number	09/826,463
Filing Date	April 5, 2001
First Named Inventor	Nobuto YAMAMOTO
Examiner Name	David S. Romeo
Art Unit	1647
Attorney Docket No.	Y1004/20017

METHOD OF PAYMENT *(check all that apply)*

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Deposit Account Name: Caesar, Rivise et al.

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) -0-

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X		=
Independent Claims		- 3** =		X		=
Multiple Dependent						=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) -0-

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	165.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 165.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Robert S. Silver	*Registration No. (Attorney/Agent)*	35,681	*Telephone*	215-567-2010
Signature				*Date*	June 28, 2004

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AF/1647

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(Substitute) PTO/SB/21 (02-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/826,463
Filing Date	April 5, 2001
First Named Inventor	Nobuto YAMAMOTO
Art Unit	1647
Examiner Name	David S. Romeo
Attorney Docket Number	Y1004/20017

Total Number of Pages in This Submission: 29

ENCLOSURES *(Check all that apply)*

- [✔] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [ ] Appeal Communication to Board of Appeals and Interferences
- [✔] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)** (In Triplicate)
- [ ] ~~Proprietary Information~~
- [ ] Status Letter
- [✔] Other Enclosure(s) (please Identify below):
  - Return Receipt Postcard
  - Letter

Remarks

Please charge Attorney Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.; Customer No. 03000 Robert S. Silver
Signature	
Date	June 28, 2004

CERTIFICATE OF TRANSMISSION/MAILING

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Typed or printed name	Robert S. Silver		
Signature		Date	June 28, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of

Nobuto YAMAMOTO

Application No.: 09/826,463

Filed: April 5, 2001

Group Art Unit: 1647

Examiner: David S. Romeo

Docket No.: Y1004/20017

For: PREPARATION OF POTENT MACROPHAGE ACTIVATING FACTORS DERIVED FROM CLONED VITAMIN D BINDING PROTEIN AND ITS DOMAIN AND THEIR THERAPEUTIC USAGE FOR CANCER, HIV-INFECTION AND OSTEOPETROSIS

BRIEF ON APPEAL

Appeal from Group 1647
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TABLE OF CONTENTS

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I. INTRODUCTION

A. Real Party in Interest

The real party in interest for this Appeal and the present application is the sole inventor, Nobuto Yamamoto.

B. Statement of Related Appeals and Interferences

There are presently no appeals or interferences, known to appellant or appellant's representatives (there is no assignee), that would directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

C. Status of Claims

Claim 22 is pending. Claim 22 stands finally rejected and is on appeal. The appealed claim is set forth in the Appendix.

D. Status of Amendments

There are no Amendments pending.

II. SUMMARY OF INVENTION

Inflammation results in the activation of macrophages. See the instant specification at page 4. This macrophage activation requires participation of B and T lymphocytes and serum vitamin D binding protein (DBP; human DBP is known as Gc protein). *Id.* *In vitro* activation of macrophages by lyso-PC requires the step-wise modification of Gc protein by β-galactosidase of lyso-Pc-treated B cells and sialidase of T cells to generate the macrophage activating factor (MAF), a protein with N-acetylgalactosamine as the remaining sugar moiety. *Id.* Thus, Gc protein is a precursor for MAF. Specification at page 5.

Incubation of Gc protein with immobilized β-galactosidase and sialidase generates remarkably high titered MAF (GcMAF). *Id.* Administration of a minute amount of GcMAF has greatly enhanced phagocytic and superoxide generating capacities of macrophages. *Id.*

Loss of the MAF precursor activity prevents generation of MAF. *Id.* Lost or reduced precursor activity of Gc protein was found to be due to deglycosylation of plasma Gc protein by α-N-acetylgalactosaminidase detected in cancer and HIV patients. *Id.* Deglycosylated Gc protein cannot be converted to MAF. *Id.* Thus, plasma α-N-acetylgalactosaminidase appears to play a role in immunosuppression in cancer and HIV patients. However, exogenously given MAF (or GcMAF) bypasses inactive (deglycosylated) Gc protein and acts directly to activate macrophages to eradicate disease (e.g., cancer, HIV).

Claim 22 on appeal is directed to a method for producing a cloned macrophage activating factor (GcMAFc), comprising cloning a Gc1 isoform into a baculovirus vector, **expressing** the cloned Gc1 isoform, contacting the cloned Gc1 isoform with immobilized β-galactosidase and sialidase, and obtaining the GcMAFc.

III. ISSUES

A. Whether the Examiner has failed to show that claim 22 is obvious under 35 U.S.C. § 103(a) as being unpatentable over Yamamoto (A) in view of Cooke (U), Quirk (U), Lichenstein (A), Murphy (B), and Luckow (V).

IV. GROUPING OF CLAIMS

There is only one claim on appeal.

V. ARGUMENT

A. Whether the Examiner has failed to show that claim 22 is obvious under 35 U.S.C. § 103(a) as being unpatentable over Yamamoto (A) in view of Cooke (U), Quirk (U), Lichenstein (A), Murphy (B), and Luckow (V).

In the Final Office Action the Examiner rejects claim 22 solely over "Yamamoto (A) in view of Cooke (U), Quirk (U), Lichenstein (A), Murphy (B), and Luckow (V)." See Final Rejection at page 2, lines 21-26. However, the Examiner still fails to show that claim 22 is obvious for the reasons discussed below.

The burden is on the Patent Office to make an initial showing of *prima facie* obviousness to support a rejection under 35 U.S.C. § 103. M.P.E.P. § 2142. According to M.P.E.P. § 2143, the three basic elements of a *prima facie* showing are: (i) there must be a suggestion or motivation to modify the applied reference and/or combine reference teachings; (ii) there must be a reasonable expectation of success in making the modification and/or combination; and (iii) the modified and/or combined teachings must teach or suggest all the claim limitations. The Office has failed to make such a showing.

(i) The proposed combination of teachings

The Final Rejection purports to show the obviousness of the pending claims by combining (1) the process of converting glycosylated Gc protein (Gc isoform) to a highly potent macrophage activating factor (GcMAF), as taught by Yamamoto; (2) the amino acid sequence of the Gc protein, and the nucleotide sequence encoding the protein, as taught by Cooke et al.; (3) the production of recombinant proteins, as taught by Quirk et al.; (4) the cloning of a novel protein, known as afamin (AFM), which belongs to the group of human serum proteins including

vitamin D binding protein, as taught by Lichenstein[1]; (5) baculovirus vectors to express glycosylated recombinant proteins late in infection, as taught by Murphy; and (6) the process for expressing exogenous proteins in insect cells using baculovirus expression vectors, as taught by Luckow.

(ii) No motivation to modify with a reasonable expectation of success

An ordinarily skilled artisan would not have had a reasonable expectation of successfully reaching the claimed invention based upon the teachings in the references cited by the examiner. To begin with, Yamamoto does not teach the cloning of the Gc protein into a baculovirus vector and Luckow teaches only generic applications regarding the use of baculoviruses as vectors. Moreover, the Office Action does not show how or where Luckow teaches that a baculovirus vector could be successfully employed to express the GcMAF protein in all insect cells. The mere fact that Luckow describes several successful examples comprising the use of a baculovirus vector to express certain proteins in insect cells, without any showing by the Office that such proteins are substantially analogous to, and reasonably predictive of, GcMAF, does not sustain the Office's burden of showing that an ordinarily skilled artisan would have been motivated to have made the proposed combination of reference teachings, and would have had a reasonable expectation of success in doing so. See, e.g., *In re Vaeck*, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991).

In fact, none of the cited references show how to clone the GcMAF or a substantially analogous protein into a baculovirus vector. Cooke discloses both the nucleotide and amino acid sequences of the vitamin D binding protein although all of the cloning was performed with

[1] Structurally, Gc protein is o-glycosylated, while all other serum proteins are not. Thus, the afamin protein is not analogous to Gc protein).

standard plasmid vectors in bacteria. Lichenstein discloses the cloning of a novel member of the human serum albumin protein family; however, it provides no guidance on how to clone the GcMAF protein of the present invention. The Gc protein is a soluble membrane protein unlike the albumin protein which is a serum protein. Also, Lichenstein neither mentions nor teaches the use of baculovirus vectors for cloning and expression purposes. The Examiner referred to Lichenstein as stating that "host cells from mammals, prokaryotes, fungi, yeast, insects and the like are used for the recombinant expression of AFM." (column 13, lines 52-55). However, merely stating that something is possible does not render it so. This statement was made as a general comment in the background section of this patent and there is no evidence in Lichenstein to support it. The only type of cloning that is performed in Lichenstein is with the use of a bacterial expression vector, not a baculovirus vector. Also, Quirk teaches how to express and purify human serum albumin in brewer's yeast. As such, it provides no teaching of how to clone GcMAF or any members of the human serum protein albumin (ALB) family with the use of a baculovirus vector. All members of the albumin family are not o-glycosylated. Even serum proteins are not o-glycosylated and thus Gc protein is unique.

The Examiner also cites Murphy as providing vectors to express recombinant proteins during baculovirus infection. Specifically, Murphy discloses several baculovirus vectors that are useful in generating glycosylated proteins in the late term of infection. As the Examiner pointed out in the Final Rejection (page 5, lines 10-11), Murphy states that these vectors may be useful for the expression of a wide variety of proteins, including blood proteins. However, the only protein that Murphy expressed with this method is the gp120 HIV glycoprotein. Unlike the Gc protein, gp120 is not sialylated and there is no evidence in Murphy to suggest that a sialylated protein could be generated as easily in insect cells. Also, there are some baculovirus infected

insect cells that do not produce sialylated proteins efficiently unless they are genetically engineered to do so (i.e., transfection with sialyltransferase or a sialic acid synthetase). In fact, Luckow at pages 15-16 acknowledges the unpredictability of foreign glycosylated protein expression by baculovirus vectors:

> Differences in the microheterogeneity of oligosaccharide structures are often observed for mammalian glycoproteins expressed in different mammalian cell lines or by individual cell lines under different culture conditions, which may or may not reflect the structure or heterogeneity of the protein in its "native" environment.

Taken together, these references hardly provide the type of teaching that would cultivate confidence in a skilled artisan, and serve as the basis for a reasonable expectation of success in cloning the Gc protein in a baculovirus vector.

The present facts are sufficiently similar to those of *Vaeck* to warrant a discussion of the case, and how the Federal Circuit's holding in that case should guide the Board's decision in this appeal. In *Vaeck*, the Federal Circuit reversed the obviousness rejection of claims to a chimeric gene capable of being expressed in Cyanobacteria cells, comprising (1) a nucleotide promoter region effective for expression in Cyanobacteria, and (2) a nucleotide fragment coding for an insecticidally active protein. *Vaeck* at 1439-40. The Office had rejected the claims as being obvious over prior art that taught the expression in Cyanobacteria of a chimeric gene comprising (1) a nucleotide promoter region effective for expression in Cyanobacteria, and (2) a nucleotide fragment coding for chloramphenicol acetyl transferase (CAT), an antibiotic resistance-conferring gene used as a marker. *Id.* The court found that the Office had not established the *prima facie* obviousness of the claimed subject matter because:

> The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in [the primary reference] of

> substituting in the disclosed plasmid a structural gene encoding Bacillus insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

Vaeck at 1443.

Thus, here as in *Vaeck*, there is no showing of *prima facie* obviousness because there is no showing by the Examiner that the applied art suggests a reasonable likelihood of success in substituting the structural gene encoding Gc protein for the structural genes which Luckow discloses have been successfully incorporated into baculovirus vectors. Luckow and Murphy are integral to the Examiner's rejection, as they are the only cited references that disclose the use of a baculovirus vector for cloning. The Examiner bases his purported *prima facie* case on the proposition that Luckow teaches that the baculovirus vector is a universally effective expression vector for all structural genes. However, as stated above, this is not what Luckow teaches.

As in *Vaeck*, it is incumbent upon the Examiner to show that Luckow discloses the successful expression of a gene sufficiently similar to the Gc protein-encoding gene that one of ordinary skill in the art would have had a reasonable expectation of successfully expressing Gc protein in a baculovirus vector.

(iii) Further significance of claim 22 over the applied art

The peptide sequence of GcMAF is the peptide sequence of native plasma Gc protein, as opposed to a mutant form of GcMAF. Thus, the peptide of GcMAFc should be the same peptide of native plasma Gc protein before treatment with immobilized β-galactosidase and sialidase. Protein synthesis in the cloning apparatus occasionally yields mutant Gc peptides having an amino acid substitution due to mistakes made during gene copying processes. However, most of

these mutant Gc peptides become functional GcMAFc obtained after treatment of these mutant peptides with immobilized β-galactosidase and sialidase and, therefore, are likely to be immunogenic (anaphylactic) in humans. Thus, only the cloned Gc protein having the wild type peptide sequence is to be used to generate the cloned GcMAFc of this invention. None of the references cited by the Examiner make this distinction.

VI. CONCLUSION

The applied references do not properly combine to anticipate or render obvious the claimed invention. Accordingly, the Honorable Board of Patent Appeals and Interferences is respectfully requested to the claim rejection and pass this application on to issuance.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD

June 28, 2004

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Attachments:
In re Vaeck
Appendix

In re Vaeck

U.S. Court of Appeals Federal Circuit
20 USPQ2d 1438

Decided October 21, 1991
No. 91-1120

Headnotes

PATENTS

1. Patentability/Validity - Obviousness - Combining references (§ 115.0905)

Rejection of claimed subject matter as obvious under 35 USC 103 in view of combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that such person would have reasonable expectation of success; both suggestion and reasonable expectation of success must be founded in prior art, not in applicant's disclosure.

2. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Patent and Trademark Office has failed to establish prima facie obviousness of claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, since prior art does not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill

reasonable expectation of success in doing so; expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious expression of unrelated genes in cyanobacteria for unrelated purposes.

3. Patentability/Validity - Specification - Enablement (§ 115.1105)

JUDICIAL PRACTICE AND PROCEDURE

Procedure - Judicial review - Standard of review - Patents (§ 410.4607.09)

Specification must, in order to be enabling as required by 35 USC 112, first paragraph, teach person skilled in art to make and use invention without "undue experimentation," which does not preclude some experimentation; enablement is question of law which is reviewed independently on appeal, although such determination is based upon underlying factual findings which are reviewed for clear error.

PATENTS

4. Patentability/Validity - Specification - Enablement (§ 115.1105)

Patent and Trademark Office did not err in rejecting, as non-enabling pursuant to 35 USC 112, first paragraph, claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, in view of relatively incomplete understanding of biology of cyanobacteria as of applicants' filing date, as well as limited disclosure by applicants of particular cyanobacterial genera operative in claimed invention, since there is no reasonable correlation between narrow disclosure in applicants' specification and broad scope of protection sought in claims encompassing gene expression in any and all cyanobacteria.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent, serial no. 07/021,405, filed March 4, 1987, by Mark A. Vaeck, Wipa Chungjatupornchai, and Lee McIntosh (hybrid genes incorporating a DNA fragment containing a gene coding for an insecticidal protein, plasmids, transformed cyanobacteria expressing such protein and method for use as a biocontrol agent). From decision rejecting claims 1-48 and 50-52 as unpatentable under 35 USC 103, and rejecting claims 1-48 and 50-51 for lack of enablement, applicants appeal. Affirmed and part and reversed in part; Mayer, J., dissents with opinion.

Attorneys:

Ian C. McLeod, Okemos, Mich., for appellant.

Teddy S. Gron, associate solicitor (Fred E. McKelvey, solicitor and Richard E. Schafer, associate solicitor, with him on brief), for appellee.

Judge:

Before Rich, Archer, and Mayer, circuit judges.

Opinion Text

Opinion By:

Rich, J.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 USC 103, as well as the rejection of claims 1-48 and 50-51 under 35 USC 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

BACKGROUND

A. *The Invention*

The claimed invention is directed to the use of genetic engineering techniques 1 for production of

proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus* proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.

As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote 2 kingdom, the

cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within transformed 3 cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.

More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing 4 the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.

The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:

1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:

(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and

(b) at least one DNA fragment coding for an insecticidally active protein produced by a Bacillus strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,

the DNA fragments being linked so that the gene is expressed.

Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers. 5 Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which expresses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

B. *Appellants' Disclosure*

In addition to describing the claimed invention in generic terms, appellants' specification

discloses two particular species of *Bacillus* (*B. thuringiensis, B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis, Anacystis, Synechococcus, Agmenellum, Aphanocapsa, Gloecapsa, Nostoc, Anabaena* and *Ffremyllia*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis,* linked to (2) a particular promoter, the P $_L$promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P $_L$promoter.

C. *The Prior Art*

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns, 6 the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT). 7 Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

Sekar I, 8 Sekar II, 9 and Ganesan 10 collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium, B. subtilis* and *E. coli.*

Friedberg 11 discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O $_L$P $_L$operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis* ...."

Miller 12 compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases 13 purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli.*

Nierzwicki-Bauer 14 identifies in the cyanobacterium *Anabaena* 7120 the start site for

transcription of the gene encoding *rbc* L, the large subunit of the enzyme ribulose-1, 5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.

Chauvat 15 discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

Reiss 16 studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

Kolowsky 17 discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.

Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

D. *The Grounds of Rejection*

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 USC 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus,* and the advantages of expressing such genes in heterologous 18 hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the

expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was prima facie obvious.

Additional rejections were entered against various groups of dependent claims which we need

not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above. The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 USC 112, first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) 19 and (z) 20 as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided in the specification. With respect to unpredictability, the examiner stated that

he cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis, Anacystis, Synechococcus, Agmenellum, Nostoc, Anabaena,* etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera. Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970)."

OPINION

A. *Obviousness*

We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 USC 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff,* 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990).

[1] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of

ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

[2] We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli.* While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed *bacterial* hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae. 21 Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these

additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell,* this court affirmed an obviousness rejection of a claim to a method for

producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 USPQ2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 USPQ2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.

....

... Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 USPQ2d at 1679-80.

In contrast with the situation in *O'Farrell,* the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior

art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. *Enablement*

[3] The first paragraph of 35 USC 112 requires, *inter alia,* that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 USPQ2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 USPQ2d at 1402.

In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

[4] Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification).

22 Accordingly, we affirm the § 112 rejection as to those claims.

In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt,* 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, 23 to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. *See Fisher,* 427 F.2d at 839, 166 USPQ at 24. In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.

Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera *Anacystis* and *Synechocystis.* Claim 48, which depend from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria. Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

CONCLUSION

The rejection of claims 1-48 and 50-52 under 35 USC 103 is *reversed.* The rejection of claims 1-46 and 50-51 under 35 USC 112, first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed.*

AFFIRMED-IN-PART, REVERSED-IN-PART

Footnotes

Footnote 1. Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell,* 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988), and are not repeated here.

Footnote 2. All living cells can be classified into one of two broad groups, procaryotes and eucaryotes. The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus

wherein their DNA resides.
Footnote 3. "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part of the host cyanobacteria, to be replicated as new cyanobacteria are generated.
Footnote 4. "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of DNA) via messenger RNA to ribosomes where a specific protein is made.
Footnote 5. In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.
Footnote 6. *Nucleic Acids Res.* 8917 (1984).
Footnote 7. Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.
Footnote 8. *Biochem. and Biophys. Res. Comm.* 748 (1986).
Footnote 9. *Gene* 151 (1985).
Footnote 10. *Mol. Gen. Genet.* 181 (1983).
Footnote 11. *Mol. Gen. Genet.* 505 (1986).
Footnote 12. *J. Bacteriology* 246 (1979).
Footnote 13. RNA polymerase, the enzyme responsible for making RNA from DNA, binds at specific nucleotide sequences (promoters) in front of genes in DNA, and then moves through the gene making an RNA molecule that includes the information contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.
Footnote 14. *Proc. Natl. Acad. Sci. USA* 5961 (1984).
Footnote 15. *Mol. Gen. Genet.* 185 (1986).
Footnote 16. *Gene* 211 (1984).
Footnote 17. *Gene* 289 (1984).
Footnote 18. Denotes different species or organism.
Footnote 19. MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:
In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure....
Footnote 20. MPEP 796.03(z), "Undue Breadth," provides in part:
n applications directed to intentions in arts were the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol,* 1938 C.D. 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield,* 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...

Footnote 21. *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Procaryotae"). Procaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom; Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).

Footnote 22. The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan,* 559 F.2d 595, 605-07, 194 USPQ 527, 536-38 (CCPA 1977). *See also United States Steel Corp. v. Phillips Petroleum Co.,* 865 F.2d 1247, 1251, 9 USPQ2d 1461, 1464 (Fed. Cir. 1989) (citing *Hogan*); *Hormone Research Found., Inc. v. Genentech, Inc.,* 904 F.2d 1558, 1568-69, 15 USPQ2d 1039, 1047-48 (Fed. Cir. 1990) (directing district court, on remand, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of *Fisher*), *cert. dismissed,* — U.S. —, 111 S. Ct. 1434 (1991). We therefore do not consider the effect of *Hogan* and its progeny on *Fisher* 's analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher,* 427 F.2d at 839, 166 USPQ at 24.

Footnote 23. The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi,* 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

Dissenting Opinion Text

Dissent By:

Mayer, J., dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co.,* 832 F.2d 581, 584, 4 USPQ2d 1621, 1624 (Fed. Cir. 1987); *Eaton Corp. v. Appliance Valves Corp.,* 790 F.2d 874, 877, 229 USPQ 668, 671 (Fed. Cir. 1986). But that is precisely what the court has permitted here. The PTO conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if thought this opinion were more persuasive than the board's, I could not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co.,* 383 U.S. 1, 17, 148 USPQ 459, 467 (1966); *Jurgens v. McKasy,* 927 F.2d 1552, 1560, 18 USPQ2d 1031, 1037 (Fed. Cir. 1991). And "[w]here there are two permissible views of

the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City,* 470 U.S. 564, 574 (1985). The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff,* 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990); *In re Kulling,* 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1057 (Fed. Cir. 1990). There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.

- End of Case -

APPENDIX: APPEALED CLAIM

A process for producing a cloned macrophage activating factor (GcMAFc) comprising:

(a) cloning a Gc1 isoform into a baculovirus vector;

(b) expressing the cloned Gc1 isoform, thereby producing a cloned Gc1 protein, wherein the Gc1 protein comprises approximately 458 amino acids with a molecular weight of approximately 52,000 Da and 3 distinct domains;

(c) contacting the clones Gc1 protein a molecular weight of approximately 52,000, approximately 458 amino acids and 3 distinct domains in vitro with immobilized bets galactosidase and sialidase, and

(d) obtaining the cloned macrophage activating factor (GcMAFc).